Gas Exchange

Introduction

Air is moved into and out of the alveolus by the mechanisms discussed in the last lesson. We skipped over the steps that involve oxygen's movement from alveolus to capillary and carbon dioxide's from capillary to alveolus. We covered getting oxygen to the tissues in Hematology. This lesson is focused on getting carbon dioxide from the tissues to the lungs and about gas exchange at the alveolar-capillary membrane.

We're removing the anatomy and histology and will be talking about gases, diffusion, and equations. Don't be intimidated by the presence of equations or by references to physics. The equations aren't there just to be memorized for the sake of memorizing. Instead, each serves a teaching purpose or acts as an advanced organizer. We're talking about the movement of gases at the lung. You've seen these equations before, and now we'll talk about them from the perspective of the lung.

We'll first cover the movement of oxygen, discussing the alveolar air equation, the diffusion equation, and the delivery of oxygen equation. We'll then change gears and talk about how CO_2 gets from the tissues to the alveoli, and how the alveolar-capillary membrane is primed to handle excess CO_2.

Remember from the last lesson—**air exchange** is the movement of air into and out of an alveolus, **gas exchange** is the movement of specific gases across the diffusion barrier. This lesson is about gas exchange. Specifically, O_2 and CO_2.

Partial Pressures of a Gas

Most learners have no difficulty conceptualizing a concentration and accepting that substances move down their concentration gradient. Then along comes a new term for gases— "partial pressure"— and everyone freaks out. You should see the **partial pressure** of a gas as being the same thing as the **concentration** of the gas in the air. The higher the partial pressure, the higher the concentration. And because substances move down their concentration gradient, gases will move down their partial pressure gradient. The reason we must use partial pressure instead of concentration is that the partial pressures of all the gases in the air need to add up to the total pressure.

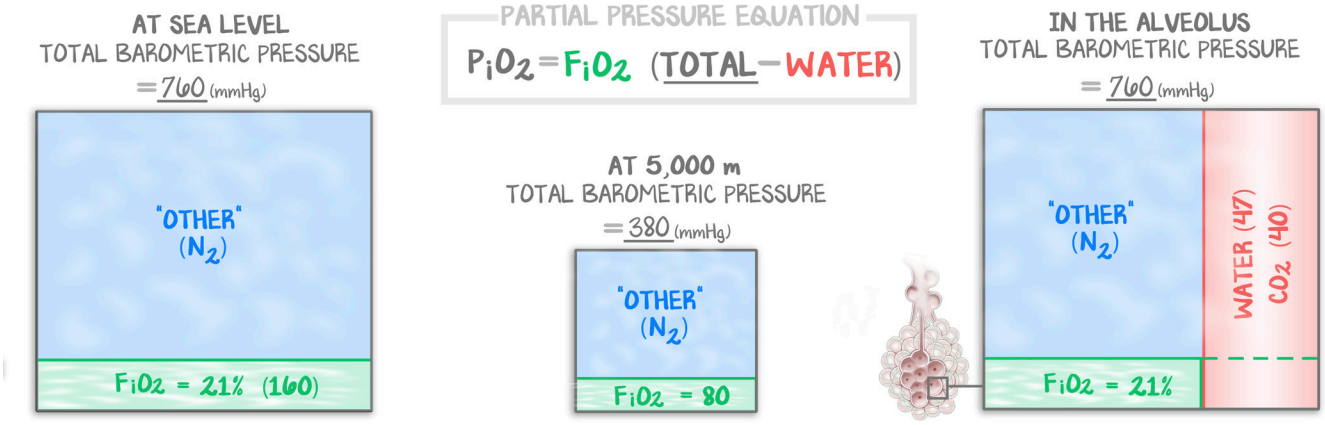

Figure 3.1: Partial Pressure Equation
There is always 21% oxygen in the air (unless you add supplemental oxygen, of course). That means the amount of oxygen in air depends on how much room there is (total pressure of air) and what else is in that air (other gases take up space). At sea level, there is 760 mmHg of total pressure, 21% of which is 160 mmHg. At a height of 5000 m, there is a total pressure of 650 mmHg, 21% of which is 135 mmHg. That's the "how much room there is" bit. When we breathe air, water vapor from our respiratory tract is added to the air, moistening it. The added water vapor takes up some of the total room from oxygen. At sea level, that partial pressure is 47 mmHg, meaning there's only 713 mmHg available for everything else, and 21% of that is about 150 mmHg.

The **total barometric pressure** of air at sea level is 760 mmHg. That's the total pressure. All the gases dissolved in that air have partial pressures, a portion of the total barometric pressure. Atmospheric air is ~21% oxygen. And so, if you are at sea level and are breathing atmospheric air, about 160 mmHg (760 × 0.21) of the total pressure is oxygen. So a "concentration" of oxygen of 160 enters the trachea. But 160 doesn't reach our alveoli. The reason is that when we inhale air, it gets warmed and humidified by our tissues. **Water vapor** is added to the air by our conducting airways, and thus takes up some of the total pressure of air, reducing what's left over for the partial pressure of oxygen. The vapor pressure is about 47 mmHg. The vapor pressure, the partial pressure of water, is 47 mmHg at 37°C at sea level. This determines the concentration of **inspired oxygen**, the partial pressure of inspired oxygen in the alveolus, which we will use below as $\mathbf{P_iO_2}$.

Alveoli to RBCs

This is where we would start talking about Fick's diffusion equation for a gas. But we're not going to put up the same old Fick equation as every other text. We're just going to use what you already know from our curriculum. You can use the diffusion equation you learned in General Physiology here. The diffusion of a thing is proportional to its solubility, surface area, and concentration gradient, and inversely proportional to the thickness of the distance that thing must travel. That is the diffusion equation, the one diffusion equation.

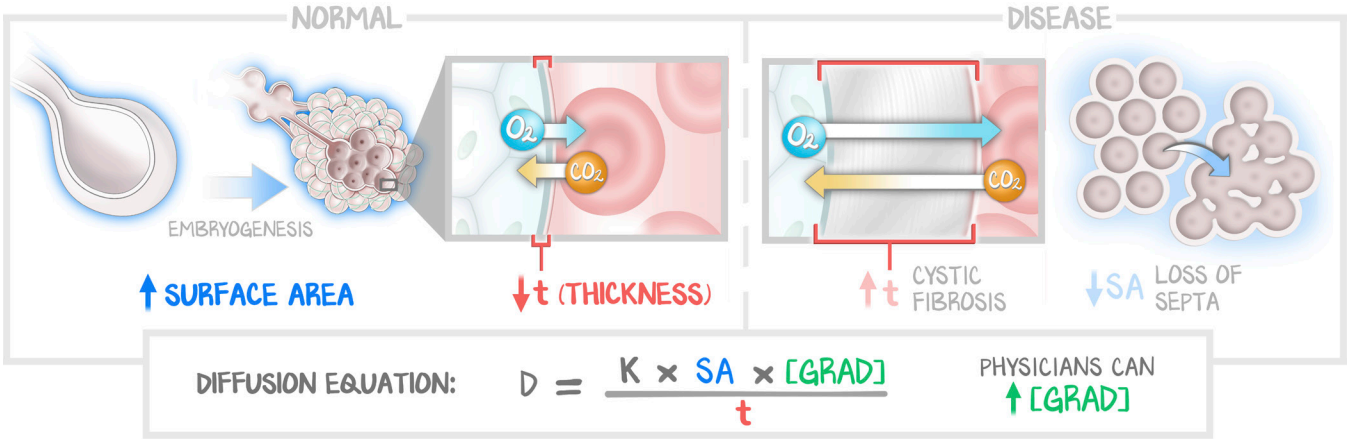

Figure 3.2: The Diffusion Barrier
The alveolar-capillary membrane is arranged to minimize the barrier to diffusion (the distance gases must travel is small) and maximize the forces of diffusion (massive surface area and concentration of gases). Oxygen has a massive diffusion force down its concentration gradient and into red blood cells, and carbon dioxide has a massive diffusion force down its concentration and into the alveoli.

The type 1 pneumocytes, the alveolar epithelium, are wafer-thin squamous cells. They are elongated and thin so as to reduce the barrier to diffusion. Surfactant covers the epithelium; the epithelium shares a basement membrane with the endothelium of a capillary in the alveolar septa. The red blood cell is inside that endothelium. The **diffusion barrier** is the thickness that the oxygen must diffuse through. That thickness is two cells (pneumocyte, endothelial cell), one basement membrane, and one layer of surfactant. The alveoli are designed to **minimize the diffusion barrier**.

The stretched-out, elongated type 1 pneumocytes that line the alveoli also maximize surface area. The terminal sacs have their surface area massively increased by adding the septa that create alveoli. The lungs are already designed to **maximize surface area**, which in turn maximizes gas exchange.

Disease can reduce the surface area or increase the diffusion barrier thickness. Fibrosis makes the septa thicker, requiring oxygen to travel farther, and so compromises diffusion. Pulmonary edema is fluid between the capillaries and the alveoli, again, increasing the diffusion barrier thickness. COPD destroys alveoli, reducing the surface area.

The only thing you can change is the **concentration gradient**. The F_iO_2 is 21% of air. The driving force is the 150 mmHg that ends up in the alveolus, pushing oxygen into the capillaries. If the person is hypoxemic, what do you do? You give them oxygen. Why? To increase the diffusion force to get more oxygen into their blood. So if there is an impaired diffusion barrier (fluid, fibrosis), or if there is impaired surface area (COPD), the way you treat that defect in the diffusion equation is by giving the patient the only thing you can control within the diffusion equation: you increase the concentration gradient by giving supplemental oxygen.

Diffusion Limited vs. Perfusion Limited

There are two types of gas: those that equilibrate quickly, and those that do not. Blood is constantly flowing through the lungs, so there is not always sufficient time for all gases to reach equilibrium. If somehow the blood was able to stay next to an alveolus that also did not exchange its air, eventually all gases would equilibrate. But in a living person, blood moves through the lungs fairly fast (5 L/min), so there may not be sufficient time to reach a balance. Those gases that do equilibrate between the capillary and alveolus are said to be **perfusion limited**. Those gases that do not equilibrate between the capillary and the alveolus are said to be **diffusion limited**. The two classic examples are carbon monoxide and nitric oxide.

Carbon monoxide is a gas that moves sluggishly through the capillary-epithelium barrier (unless inhaled in large amounts, like mouth-on-an-exhaust-pipe). If the blood were left to sit there and not move, CO would balance. However, since blood continues to move through the lungs, CO never has the chance to balance out. Thus, CO is said to be **diffusion limited**: changing the perfusion will not change the CO in the body via the lungs; only an increase in the partial pressure gradient can increase rates of uptake. Only by using the principles of the diffusion equation can a change in absorption occur.

Nitric oxide is a gas that moves through the capillary-epithelium barrier very rapidly and does not combine with elements in the blood. Thus, very quickly, NO has no further driving force across the membrane. The only way to get more NO into the blood is to bring in FRESH blood. As new blood comes in and kicks the old (saturated) blood out, NO can quickly reach equilibrium between the new blood and the alveoli. NO is said to be **perfusion limited**: only increases in perfusion (flow) can lead to an increase in NO in the body via the lung.

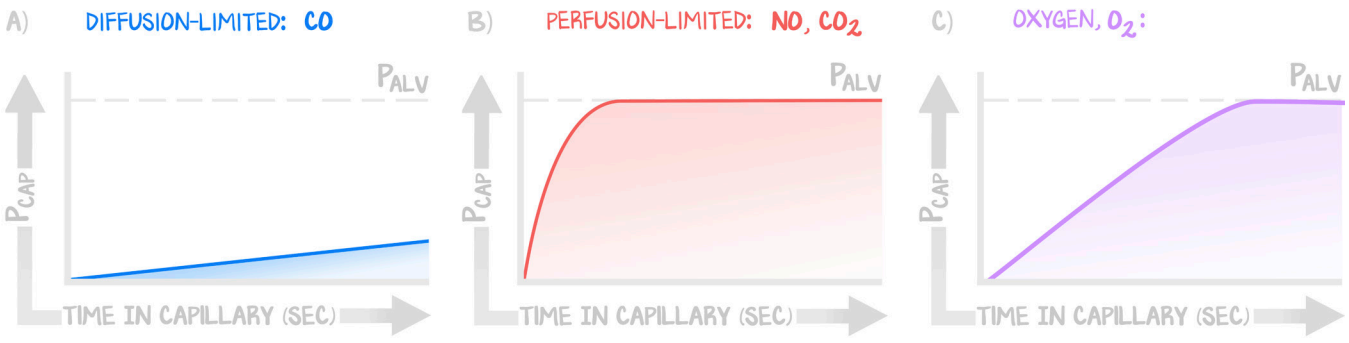

Figure 3.3: Diffusion- vs. Perfusion-Limited Gases
A diffusion-limited gas is one that will not equilibrate between the alveolus and the capillary in the time the red blood cell is present in the capillary of the alveolus. A diffusion-limited gas's diffusion can be improved by manipulating the diffusion equation. A perfusion-limited gas is one that readily equilibrates in the capillary. Here, altering the diffusion equation's forces will not improve equilibration, nor will increased perfusion allow for more rapid equilibration. But losing vasculature causes perfusion-limited gases to accumulate, as CO_2 does in COPD.

Oxygen Is Diffusion Limited

Oxygen is perfusion limited at rest and without disease. As we'll learn in Pulmonary: Circulation #1: *Pulmonary Circulation*, when there is an acute insult, there is an increase in cardiac output. That increase in cardiac output causes more vessels to open and be perfused in an attempt to maintain oxygen levels. That makes a lot of sense. If the heartbeat is slow and the demands of the tissue are not increased, it sounds like a good idea to have hemoglobin maximally saturate prior to the end of the capillary. That way, when the heart rate does pick up, or there is a higher demand by the tissues, there is a little reserve that can be called upon.

But oxygen's perfusion-limited quality is tenuous. It doesn't take a lot to make oxygen diffusion limited. Exercise increases the heart rate so that oxygen no longer remains perfusion limited. Any disease that impairs the oxygen diffusion equation, even just a little, will make oxygen no longer perfusion limited. And since you are going to care for people who are sick, you should learn that **oxygen is diffusion limited.** You know how you can be absolutely sure that the last statement is correct? What was your answer to the question in the last paragraph, two sections back? When oxygen levels are low, what do you do? Give oxygen. Why? To improve the **diffusion equation**, to **increase the force of diffusion.** The body responds by increasing perfusion to the alveoli because oxygen is perfusion limited in a healthy state. Providers respond to low oxygen saturation by giving oxygen because oxygen is diffusion limited in a disease state.

Alveolar Gas Equation and the A-a Gradient

Because oxygen can become diffusion limited, when someone is hypoxemic, we want to know whether it's a problem with oxygen diffusion or with oxygen getting to the alveoli. We can do that with the alveolar gas equation and the A-a gradient.

Before we get started, here is the main takeaway of the alveolar gas equation and A-a gradient. A hypoxemic patient with an **elevated A-a gradient** means oxygen is getting to the alveoli, but not from the alveoli to the blood. That means a problem with the alveoli. A hypoxemic patient with a **normal A-a gradient** means oxygen is not getting to the alveoli. This means a problem with the mechanics of ventilation.

Before we get started, here are the **two major functional limitations** of the alveolar gas equation and A-a gradient. One, the equation is wildly unreliable because the calculations rarely account for variation (often done not at sea level, not on room air). Two, the clinical scenario gives you more information about what's wrong than the A-a gradient does.

NOT GETTING OXYGEN TO ALVEOLI	NOT GETTING OXYGEN FROM THE ALVEOLI TO THE CAPILLARIES
High altitude (low partial pressure of oxygen in the air)	Every problem with the lung that causes hypoxemia
Neuromuscular disease (not moving enough air)	
Obesity hypoventilation syndrome, narcotic overdose	

Table 3.1: Functional Limitations of the Alveolar Gas Equation

So, if you are comfortable with the above paragraphs, skip down to the next section. We are going to go over some equations because it is obligatory for pulmonary physiology. In "Partial Pressures" above, we learned how we could calculate the inspired partial pressure of oxygen: total barometric pressure minus water vapor times the F_iO_2. The F_iO_2 is normally 21%.

$P_iO_2 = F_iO_2 \times (760 - 47) = \sim 150$

Some very smart people did some very smart science with some very smart rationalizing. You get the benefit of their having figured it out, so you don't have to. We are not going to derive the alveolar gas equation. We're just going to show it to you. The **alveolar gas equation** enables the calculation of the alveolar partial pressure of oxygen using the measured partial pressures of CO_2 and O_2 in an arterial sample. By obtaining an arterial blood gas, a laboratory that reports a **Pao_2** (partial pressure of oxygen in the arteries) and a **$Paco_2$** (partial pressure of carbon dioxide in the arteries), you can use the alveolar gas equation to estimate the **P_{AO_2}** (partial pressure of oxygen in the alveoli). You just also have to have the P_iO_2 correct.

$P_{AO_2} = P_iO_2 - Paco_2 / R$

By using the partial pressure equation, we can derive P_iO_2. Because CO_2 always equilibrates in the alveolus, with a blood gas, we can directly measure $Paco_2$ and therefore assume $Paco_2$. R is 0.8. With the alveolar gas equation, we can then calculate P_{AO_2}; the oxygen number the capillary should equilibrate to if there were nothing wrong with the diffusion barrier. With the alveolar gas equation, we can then deduce the alveolar-arterial gradient, the **A-a gradient**.

$P_{AO_2} - Pao_2 =$ A-a gradient

The A-a gradient should be between 0 and 10 mmHg. It isn't 0 mmHg because the lung's perfusion and ventilation are not perfectly aligned (Pulmonary: Circulation #1: *Pulmonary Circulation*). If it is high, it's a diffusion barrier problem (i.e., lungs). If not high, it isn't a diffusion barrier problem (i.e., ventilation). The thing is, you don't start considering a workup from the A-a gradient. The person who has pinpoint pupils, a respiratory rate of 2, and is comatose gets naloxone to reverse their opiate overdose. They would be hypoxemic and have a normal A-a gradient. The person who has ground-glass opacities on their X-ray and a restrictive pattern on their PFTs has pulmonary fibrosis—you know they are going to have an elevated A-a gradient before you look.

The alveolar air equation and A-a gradient are favorites of academics. **Do not use the A-a gradient in practice.** All it tells you is, "lung vs. not lung." And that was a lot of words, and a lot of paper real estate, to arrive at a conclusion so simple.

Oxygen Delivery Equation; Getting Oxygen from Lung to Tissues

We covered the oxygen delivery equation in Heme/Onc when we talked about hemoglobin. There we simplified the equation. Here we represent the equation in its entirety. **Hemoglobin** is the main transport mechanism of oxygen. A very small percent is **dissolved in plasma**. When you get an arterial blood gas and monitor the partial pressure of oxygen, you are assessing the partial pressure of oxygen **in plasma**. The highest it should ever be is 100 mmHg. Normal is around 80 mmHg. Having excess oxygen in the plasma means that the hemoglobin is supersaturated, and the excess oxygen in the plasma will only induce free radical formation and worsen the patient's outcome.

A normal oxygen saturation (monitored with a finger probe) is 99%. A normal Pao_2 is about 80 mmHg. You can estimate the Pao_2 (obtained by sticking a needle in someone's artery) by knowing the pulse ox—pulse ox minus 20. But that only works if there isn't 100% saturation, because Pao_2 plus 20 should be the %saturation. But if the Pao_2 is 436, and you add 20 to that, you get 456 . . . but the pulse ox can't go above 100%. A Pao_2 above 100 mmHg is also indicative of oxygen toxicity, and the supplemental oxygen should be taken way down.

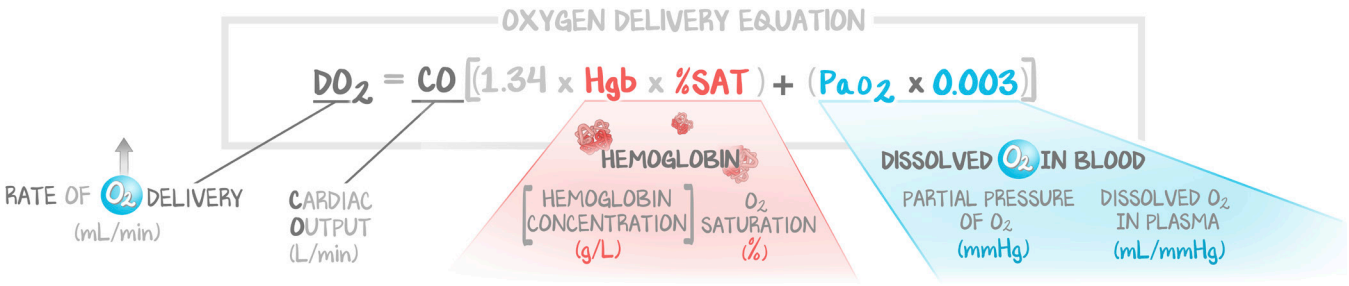

Figure 3.4: Oxygen Delivery Equation for Real
A simplified version was shown in Hematology/Oncology. This is the real one. Cardiac output, hemoglobin, and %saturation remain the same. But now we add in a 1.34 (you don't have to know where this comes from) and a Pao_2 component. The %saturation is how saturated with oxygen hemoglobin is. That's the main way of moving oxygen in the blood. Pao_2 is how much oxygen is dissolved in the plasma. It contributes very little to oxygen delivery (× 0.003) but gives some important diagnostic clues. The best way to treat a patient with impaired oxygen delivery to tissues is to increase their ability to transport oxygen—transfuse blood. You administer oxygen to a patient with a low oxygen saturation to bring it closer to normal. Raising the plasma oxygen concentration above normal levels leads to oxygen toxicity and barely does anything for oxygen delivery. First give oxygen, but the treatment for poor oxygen delivery is blood.

When more oxygen is needed, cardiac output increases, heart rate goes up, and contractility goes up. The hemoglobin cannot change acutely, and the saturation of hemoglobin approaches 100% normally. The only acute response to oxygen demands is to kick up the cardiovascular system. The only acute response to oxygen demands by a health care provider is to add supplemental oxygen, increasing the saturation of hemoglobin and the oxygen content of plasma.

Getting Carbon Dioxide from Tissues to Lung

CO_2 is a waste product of metabolism, of aerobic metabolism. Red blood cells bring oxygen and glucose to tissues so those tissues can use that oxygen and glucose for glycolysis, the Krebs cycle, and the electron transport chain. The thing the tissues make with that oxygen, through the process of cellular respiration, is carbon dioxide. Red blood cells bring the oxygen and glucose, then take care of what the tissues make with that oxygen and glucose. "Take care of" is not just "carry," like the RBCs do with oxygen. Carbon dioxide is transported back to the lungs by three mechanisms—as bicarbonate in the blood, carbaminohemoglobin bound to deoxyhemoglobin, and regular old CO_2 dissolved in the plasma. The mechanisms are interrelated, and each mechanism also influences oxygen dissociation from hemoglobin. It is more than just coincidence or convenience that the RBC brings O_2 and takes care of CO_2—one influences the other.

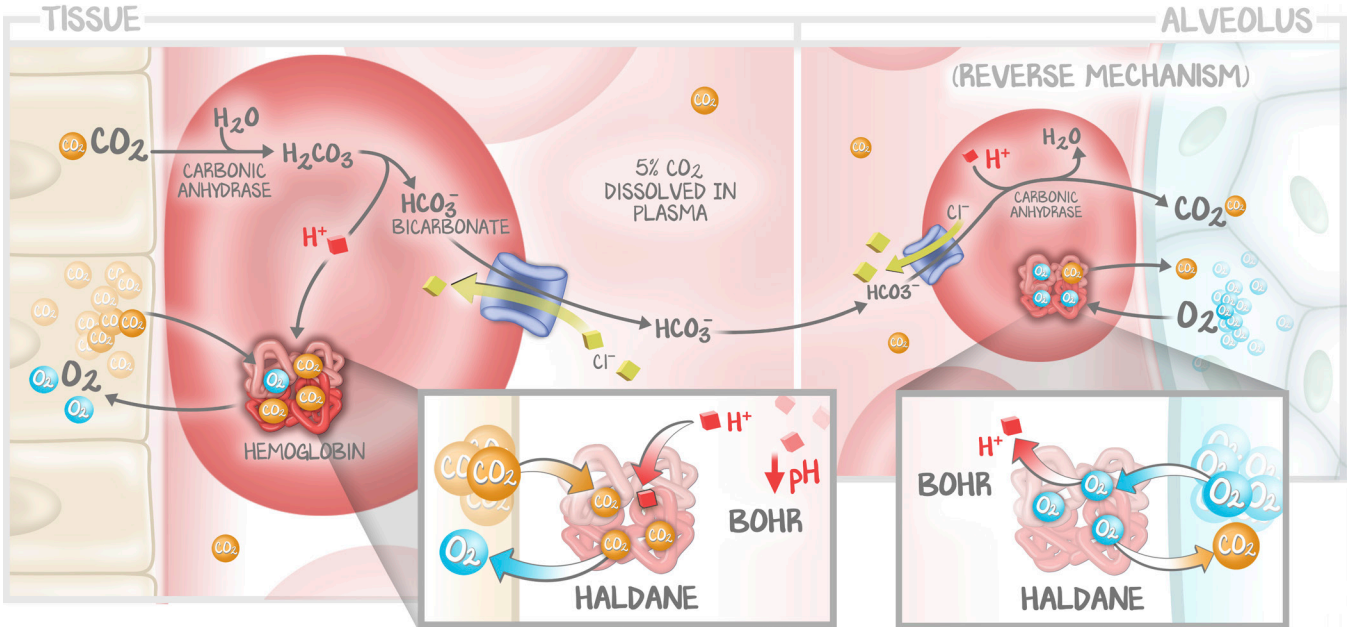

Figure 3.5: Red Blood Cell and CO_2
The red blood cell brings oxygen to the tissues. It also takes CO_2 away. It does that through several simultaneous mechanisms. Refer to this figure as we discuss the next several paragraphs.

1. Bicarbonate. Most of the CO_2 in the blood is carried as bicarbonate. CO_2 comes out of the tissues and into the red blood cells. **Carbonic anhydrase** (the same enzyme as is seen all over the curriculum) in red blood cells combines CO_2 and H_2O to form carbonic acid (H_2CO_3). Carbonic acid rapidly dissociates into **bicarbonate and hydrogen ions**. The bicarbonate (HCO_3^-) has a negative charge. Chloride has a negative charge. Bicarbonate is exchanged for chloride and is released into the plasma by the red blood cells using a bicarbonate-chloride antiporter. This channel ensures electroneutrality and uses chloride's concentration gradient to drive the reaction. Bicarbonate is left to float in the plasma until it gets to the lungs, where the same carbonic anhydrase combines the hydrogen ion with the bicarb, forming water and CO_2, after which the CO_2 diffuses into the alveoli to be exhaled.

That process just left a H^+ ion behind in the cytoplasm of the red blood cell. H^+ accumulation in a cell is bad. We call that acidosis. So, the red blood cell must do something with that hhydrogen ion. The red blood cell asks hemoglobin to hold onto it for a while as H^+Hgb.

H^+Hgb. Because of the positive cooperativity of the red blood cell we discussed in Heme/Onc, as hemoglobin unloads oxygen, its affinity for oxygen goes down. This is a mechanism by which red blood cells are sure to unload oxygen in the tissues but hold onto it through the arterial system. **Deoxyhemoglobin** has the ability to buffer H^+. In doing so, it further reduces the affinity of hemoglobin for oxygen. That means as oxygen is unloaded from hemoglobin, hemoglobin more readily unloads oxygen and more readily binds H^+, which in turn makes oxygen even more likely to be unloaded. The decreased affinity of hemoglobin for oxygen when bound to hydrogen ion is called the **Bohr effect**. This is why CO_2 and acid cause a right-shift of the oxygen dissociation curve.

2. Carbaminohemoglobin. Carb-amino-hemoglobin is what you call hemoglobin when it gets a CO_2 stuck onto an amine group. Any protein can do this, but because hemoglobin is so abundant in the blood and optimized for it to happen, hemoglobin gets the credit. Thus, carbaminohemoglobin is the main way CO_2 rides on proteins back to the lungs. As oxygen is unloaded from hemoglobin, the affinity for oxygen goes down. As oxygen is unloaded from hemoglobin, **hemoglobin's affinity for CO_2 goes up**. The reverse is true also, that as hemoglobin becomes more and more oxygenated, its affinity for CO_2 goes down. This phenomenon is known as the **Haldane effect**.

So let's just analyze what happens. A red blood cell leaves the lungs, loaded with oxygen. It arrives at immensely active tissue—CO_2 is in abundance, and O_2 is running out. The concentration gradient is massive for oxygen to be unloaded to the tissues. As it does, positive cooperativity induces a conformational change that makes oxygen more likely to be unloaded, and more oxygen comes off of hemoglobin. At the same time, there is a tremendous concentration gradient that drives CO_2 out of the tissues and into the red blood cell. Carbonic anhydrase makes some bicarbonate and hydrogen ions from that CO_2. The hydrogen ions bind to hemoglobin, causing its affinity for oxygen to go even lower, so more oxygen leaves into the tissue (Bohr). As the hemoglobin loses its oxygen and affinity for oxygen, it gains affinity for CO_2, forming carbaminohemoglobin (Haldane).

The red blood cell leaves the tissues and arrives at the lungs. Oxygen is plentiful in the alveolus, and there is a massive driving force sending oxygen to the hemoglobin. As oxygen saturates hemoglobin, its affinity for oxygen increases, so more oxygen binds to hemoglobin. As it does, the affinity for CO_2 lessens, and so the hemoglobin (as carbaminohemoglobin) releases CO_2 (Haldane effect). The binding of oxygen to hemoglobin lessens hemoglobin's affinity for H^+ (Bohr), liberating H^+ ions that are combined with circulating bicarbonate by carbonic anhydrase in the red blood cell. Carbonic anhydrase makes water and CO_2. All that CO_2 leaves the blood into the alveolus.

3. CO_2 dissolved in plasma. Whatever small amount of CO_2 the red blood cells don't handle through the magic of the previous few paragraphs is dissolved in the plasma. About 5% of CO_2 is managed this way.

CO_2 is Perfusion Limited

CO_2 is perfusion limited. There is a partial pressure of **0 mmHg in the alveolar air** and a variable amount of returning CO_2 in the venous blood. There is a massive driving force for CO_2 to leave the blood and enter the alveoli. Unlike oxygen, CO_2 is always perfusion limited. Instead, what becomes an issue is the **trapping of air** within the alveoli. While there may be no difficulty getting the CO_2 into the alveolus, if there is trouble getting the air with CO_2 out of the airway, there will be an accumulation of CO_2 in the alveolus, and thus a loss of diffusion force.

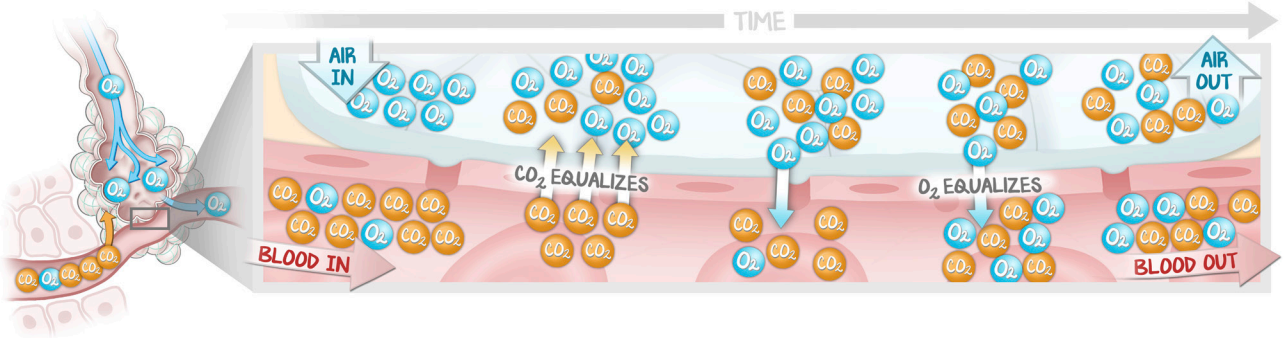

Figure 3.6: CO_2 Is Perfusion Limited
There is essentially no CO_2 in inspired air. Because CO_2 is perfusion limited, it readily equilibrates with the alveoli. For the majority of the length of the capillary CO_2 doesn't move into our out of the alveolus. Even if the blood sped through this capillary faster than physiologically possible, CO_2 would still equilibrate. O_2, on the other hand, does eventually equilibrate, but requires the length of the capillary to do so. If blood sped through this capillary faster than normal (not physiologic possible), O_2 would have difficulty with equilibration.

Getting CO_2 out of the Person; the Alveolar Ventilation

The **minute ventilation** is the volume of air breathed with each breath multiplied by the respiratory rate. It's an easy thing to ballpark when you're standing at the bedside, and it's something you can easily manipulate with a ventilator. It requires no extra equipment or equations to deduce. And so, what we'll teach you in clinicals is that to decrease a patient's CO_2, you increase the minute ventilation. That means turning up either the respiratory rate or the tidal volume. But this isn't clinicals.

The thing you care about at the Basic Sciences level is **alveolar minute ventilation**, which is simply called alveolar ventilation. Because only the alveolar volume can participate in gas exchange, and alveolar volume is all the tidal volume not the dead space, the alveolar minute ventilation is the alveolar volume (tidal volume minus dead space volume) times the respiratory rate. There are lots of equations and lots of techniques to actually measure dead space and alveolar minute ventilation. You won't need to do them. Instead, we can use the alveolar ventilation equation to talk about the causes of **hypercapnia** and justify what the human body does in response to hypercapnia.

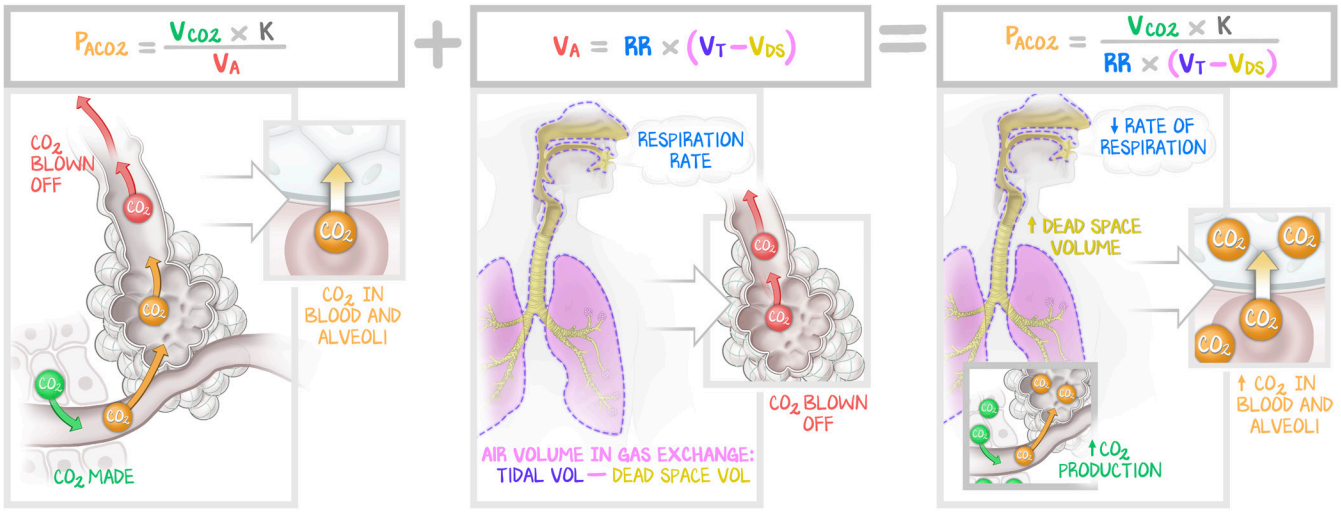

Figure 3.7: Alveolar Ventilation Equation
Because CO_2 always equilibrates, the measured arterial $PaCO_2$ is the same as the alveolar $PACO_2$ blown off. The first equation says, the more metabolic activity you have (V_{CO2}), the more CO_2 there will be in the blood, and therefore the alveoli. The second equation explains V_A, alveolar ventilation. Since the only air the will participate in gas exchange is within the alveoli, and that alveolar volume is the tidal volume (V_T) minus dead space (V_{DS}), the volume used is (V_T-V_{DS}). Because alveolar ventilation is also based on the number of breaths per minute, that volume is multiplied by the respiratory rate. Because V_A is in the denominator, increases in V_A decrease $PACO_2$ which is the same thing as decreasing $PaCO_2$, which is the same thing as saying blowing off more CO_2. V_A can be made smaller (and thus $PACO_2$ is higher) with a slower respiratory rate (slower RR), smaller tidal volume (smaller V_T) or a decreased dead space (V_{DS}). The third equation IS the alveolar ventilation equation which serves no purpose other than to confuse learners.

That last equation in Figure 3.7 is the **alveolar ventilation equation**. It is used to explain how changes in respiratory physiology alter the amount of carbon dioxide in a person's artery. We did the following exercise in the figure caption as it related to the pieces of the equation each of the following examples influenced. We do it again from the perspective of the complete equation in the third panel. This is the utility of this equation. To demonstrate how CO_2 retention could occur, and why a person breathes harder and faster to blow off CO_2.

If there is **increased metabolism**, the CO_2 levels in the blood will rise. Thus, the numerator of the alveolar ventilation equation will increase, and there will be more alveolar air, and thus more CO_2 in the blood.

If there is an **increase in dead space**, the CO_2 levels in the blood will rise. Less volume available to exchange, less volume to get CO_2 out. Mathematically, the denominator will be a smaller number, and so there will be more alveolar CO_2 (the equation), and therefore more arterial carbon dioxide (because CO_2 equilibrates).

If there is a **decrease in tidal volume** or a **decrease in respiratory rate**, the CO_2 levels in the blood will rise. The denominator will be a smaller number, and so there will be more alveolar air, and therefore more arterial carbon dioxide.

This is a mathematical representation for the causes of hypercapnia—adding dead space, making more CO_2, or reducing minute ventilation. And there it is—the payoff. Tidal volume and respiratory rate, the **minute ventilation**, is how the body regulates carbon dioxide. If you **increase the minute ventilation,** you **reduce carbon dioxide** in the blood. If you **decrease the minute ventilation,** you **increase carbon dioxide**. But there is the caveat that simply increasing the respiratory rate to increase minute ventilation has diminishing returns—because there is dead space in the conducting airways, the frequency of the breaths is limited by the necessary volume to overcome the dead space. When you hit ventilators later in your training, you'll see that you can dial in respiratory rate and tidal volume to regulate the carbon dioxide. Regurgitating the equation is useless. Just use it to solidify the causes of hypercapnia (Basic Sciences only) and how to regulate CO_2 with a ventilatory rate (Basic Sciences and any patient who breathes for the rest of your career).